



HHS Public Access

Author manuscript

Lancet HIV. Author manuscript; available in PMC 2018 February 01.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Published in final edited form as:

Lancet HIV. 2017 February ; 4(2): e67–e73. doi:10.1016/S2352-3018(16)30215-6.

Immunological and infectious risk factors for lung cancer in US veterans with HIV: a longitudinal cohort study

Keith Sigel, MD, Prof. Juan Wisnivesky, MD, Kristina Crothers, MD, Kirsha Gordon, PhD, Sheldon T Brown, MD, David Rimland, MD, Maria C Rodriguez-Barradas, MD, Cynthia Gibert, MD, Matthew Bidwell Goetz, MD, Roger Bedimo, MD, Lesley S Park, PhD, and Prof. Robert Dubrow, MD

Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA (K Sigel MD, Prof J Wisnivesky MD, S T Brown MD); Department of Medicine, University of Washington School of Medicine, Seattle, WA, USA (K Crothers MD); Department of Medicine, VA Connecticut Healthcare System and Yale Schools of Medicine and Public Health, New Haven, CT, USA (K Gordon PhD); Infectious Diseases Section, James J Peters VA Medical Center, Bronx, NY, USA (S T Brown); Infectious Diseases Section, Atlanta VA Medical Center and Emory University School of Medicine, Decatur, GA, USA (D Rimland MD); Infectious Diseases Section, Michael E DeBakey Veterans Affairs Medical Center and Baylor College of Medicine, Houston, TX, USA (M C Rodriguez-Barradas MD); Department of Medicine, George Washington University School of Medicine and Washington DC Veterans Affairs Medical Center, Washington, DC, USA (C Gibert MD); Department of Medicine, VA Greater Los Angeles Healthcare System, Los Angeles, CA (M Bidwell Goetz MD); David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, USA (M Bidwell Goetz); Division of Infectious Diseases, VA North Texas Health Care System, Dallas, TX, USA (R Bedimo MD); Center for Population Health Sciences, Stanford University School of Medicine, Palo Alto, CA, USA (L S Park PhD); and Department of Chronic Disease Epidemiology, Yale School of Public Health, New Haven, CT, USA (Prof R Dubrow MD)

Summary

Background—HIV infection is independently associated with risk of lung cancer, but few data exist for the relation between longitudinal measurements of immune function and lung-cancer risk in people living with HIV.

Methods—We followed up participants with HIV from the Veterans Aging Cohort Study for a minimum of 3 years between Jan 1, 1998, and Dec 31, 2012, and used cancer registry data to identify incident cases of lung cancer. The index date for each patient was the later of the date HIV care began or Jan 1, 1998. We excluded patients with less than 3 years' follow-up, prevalent

Correspondence to: Dr Keith Sigel, Department of Medicine, Icahn School of Medicine at Mount Sinai, 17 East 102nd Street, New York, NY 10029, USA, keith.sigel@mssm.edu.

Contributors

KS designed the study, did the data analysis, and wrote the first draft of the Article. JW, KC, KG, STB, DR, MCR-B, CG, MBG, RB, and LSP contributed to study design, interpretation of analysis results, and writing of the Article. RD participated in data collection, study design, interpretation and modification of data analysis, and writing of the Article.

Declaration of interests

JW has received lecture honoraria from Novartis and a research grant from GlaxoSmithKline. All other authors declare no competing interests.

diagnoses of lung cancer, or incomplete laboratory data. We used Cox regression models to investigate the relation between different time-updated lagged and cumulative exposures (CD4 cell count, CD8 cell count, CD4/CD8 ratio, HIV RNA, and bacterial pneumonia) and risk of lung cancer. Models were adjusted for age, race or ethnicity, smoking, hepatitis C virus infection, alcohol use disorders, drug use disorders, and history of chronic obstructive pulmonary disease and occupational lung disease.

Findings—We identified 277 cases of incident lung cancer in 21 666 participants with HIV. In separate models for each time-updated 12 month lagged, 24 month simple moving average cumulative exposure, increased risk of lung cancer was associated with low CD4 cell count (p trend=0.001), low CD4/CD8 ratio (p trend=0.0001), high HIV RNA concentration (p =0.004), and more cumulative bacterial pneumonia episodes (12 month lag only; p trend=0.0004). In a mutually adjusted model including these factors, CD4/CD8 ratio and cumulative bacterial pneumonia episodes remained significant (p trends 0.003 and 0.004, respectively).

Interpretation—In our large HIV cohort in the antiretroviral therapy era, we found evidence that dysfunctional immune activation and chronic inflammation contribute to the development of lung cancer in the setting of HIV infection. These findings could be used to target lung-cancer prevention measures to high-risk groups.

Funding—US National Institutes of Health.

Introduction

Lung cancer is the most common non-AIDS-defining cancer and a leading cause of cancer death in people with HIV.¹⁻³ HIV infection is independently associated with risk of lung cancer after accounting for established risk factors such as age, smoking, and chronic obstructive pulmonary disease (COPD).⁴ Several factors have been tentatively linked to the increased risk of lung cancer associated with HIV infection, including immunosuppression (ie, low CD4 cell count)⁵ and recurrent lung infections.⁶

Findings from studies of the relation between severity of HIV-related immunosuppression as measured by CD4 cell count and lung-cancer risk have been mixed, with several previous studies showing an association^{5,7} and others^{8,9} no association. Many previous studies have been limited by retrospective approaches, small numbers of cases of lung cancer, an absence of data about smoking, or static, insensitive measures of immunosuppression, such as baseline CD4 cell count.

Immunosuppression places people with HIV at increased risk of bacterial pneumonia.¹⁰ An association between history of bacterial pneumonia and raised lung-cancer risk has been noted in both the general population¹¹ and people living with HIV.^{4,6} However, no investigators have previously attempted to disentangle the relations between CD4 cell count, history of bacterial pneumonia, and risk of lung cancer. In addition to low CD4 cell count, other clinically available markers of immune impairment include CD8 cell count and ratio of CD4 cell count to CD8 cell count (a low ratio has been associated with immunosenescence and abnormal immune activation in HIV-negative people¹²). In patients with HIV, a persistently low CD4/CD8 ratio has been associated with increased risk of all-cause

mortality, non-AIDS mortality, and incidence of non-AIDS-defining cancer.^{13,14} However, the ratio has not been previously assessed as a predictor of lung-cancer risk.

In this study we used data from a large, national HIV cohort from the era of antiretroviral therapy (ART) to assess the relations between lagged and cumulative markers of immune function and cumulative bacterial pneumonia episodes and risk of lung cancer.

Methods

Study population

We used data from the Veterans Aging Cohort Study (VACS), a large HIV cohort assembled from national Veterans Affairs administrative and clinical databases. The full VACS included more than 48 000 veterans living with HIV receiving Veterans Affairs care between 1996 and 2012, but we restricted our analysis to 40 973 patients receiving care between Jan 1, 1998, and Dec 31, 2012, because during this period the database contained the most complete data about immune markers. For our analysis, the index date for each patient was the later of the date HIV care began or Jan 1, 1998.

Research in context

Evidence before this study

We searched Google Scholar with the terms “lung cancer” and “HIV” for articles published in English between Jan 1, 1997, and Aug 1, 2016 (the date of our final search). We selected studies in which risk factors for lung cancer were assessed in patients living with HIV during the antiretroviral therapy era. Studies of the relation between CD4 cell count and lung-cancer risk had mixed results, and most studies included small numbers of cancer cases. Bacterial pneumonia was assessed as a risk factor for lung cancer in people with HIV in two previous studies, but this risk was not clarified in the context of immunosuppression. We found no studies in which the relation between the ratio of CD4 cell count to CD8 cell count and risk of lung cancer was examined.

Added value of this study

The Veterans Aging Cohort Study is a large US cohort of people with HIV, for whom detailed cancer and exposure data are available. We showed that cumulative low CD4/CD8 ratio, a novel risk factor for lung cancer, was the most robust independent immunological predictor of increased risk of lung cancer in this cohort. Additionally, cumulative episodes of bacterial pneumonia were directly associated with risk of lung cancer, even after immunological factors were accounted for.

Implications of all the available evidence

Our findings suggest that, in people with HIV, abnormal immune activation, as represented by low CD4/CD8 ratio, and previous episodes of bacterial pneumonia might have roles in the development of lung cancer, the leading cause of cancer death in this population. These risk factors, along with smoking history, age, and chronic obstructive

pulmonary disease, could be used to target high-risk groups with lung-cancer prevention measures, such as CT-based screening.

Because we were interested in associations between longitudinal exposures to different measures of immune function and risk of lung cancer, we further restricted the cohort by excluding patients with less than 3 years of follow-up or with a prevalent lung-cancer diagnosis (appendix p 1). We then excluded patients for whom laboratory data were incomplete during the study period. Each patient was then followed up until the date of their last available laboratory measurement (carried forward 365 days), diagnosis of lung cancer, death, or Dec 31, 2012. The Institutional Review Boards of the Veterans Affairs Connecticut Healthcare System and the Yale University School of Medicine approved this research (they waived the need for informed consent).

Procedures

We linked VACS data with the Veterans Affairs Central Cancer Registry (VACCR), which ascertains almost 90% of cancer cases diagnosed or treated by Veterans Affairs in patients living with HIV.¹⁵ We used VACCR data to identify pathologically confirmed incident cases of lung carcinoma among cohort members. We established patients' baseline characteristics on the basis of the period from 12 months before the index data until 63 months afterwards. Baseline characteristics were demographic variables (ie, age, sex, and race or ethnicity), clinical diagnoses (COPD, occupational lung disease, alcohol and drug use disorders, bacterial pneumonia, tuberculosis, and *Pneumocystis jirovecii* pneumonia) identified from relevant diagnostic codes (appendix p 2), chronic hepatitis C virus infection (based on relevant laboratory tests and diagnosis codes and considered present if found at any time during follow-up), smoking status (current, former, or never) determined from a clinical-reporting system based on previously validated methods,⁴ use of ART and specific ART drug classes identified from the Veterans Affairs pharmacy database, CD4 cell count, CD8 cell count, CD4/CD8 ratio, and HIV RNA concentration.

We collected longitudinal laboratory data for all participants during the observation period, and organised longitudinal values by the month and year in which they were reported. For months when no laboratory measures were available for a patient, we used linear interpolation to assign imputed values.¹⁶ Initial laboratory values were carried back 90 days. Final values were carried forward either 365 days or until cancer diagnosis or censoring, whichever came first. If a patient had a gap of more than 547 days between laboratory tests, the value before the gap was carried forward for 365 days and then the patient was censored.

We identified all episodes of bacterial pneumonia after the index date from inpatient admissions (>90 days apart) on the basis of relevant diagnosis codes. Longitudinal exposure was measured by cumulative counts of episodes (including baseline episodes).

Statistical analysis

We compared baseline characteristics of patients who developed lung cancer with those of patients who did not develop lung cancer during follow-up with the Wilcoxon rank-sum test for age, the χ^2 test, or Fisher's exact test, as appropriate, for non-ordinal categorical

variables, and the Cochran-Armitage test of trend for ordinal categorical variables (such as CD4 cell count categories). We then created new time-updated longitudinal variables for our immune markers of interest to capture either lagged exposures at single timepoints or lagged cumulative exposures. To estimate lagged exposure, we used time-updated lagged values (12, 24, and 36 months); we lagged by no less than 12 months to minimise reverse causality (ie, lung-cancer diagnosis affecting the time-updated exposure) and to capture exposures that occurred before clinical lung cancer. To estimate cumulative exposure, we used simple moving averages (SMAs), because cumulative averages would have been biased by the shorter follow-up times for patients with lung cancer. SMAs are frequently used in econometric analysis to capture mean data values during a rolling, finite period, and have been applied to similar analyses of immunological measurements and HIV-related outcomes.¹⁷ We also lagged time-updated measures of cumulative exposure: 12 month lagged, 12 month SMAs; 12 month lagged, 24 month SMAs; and 24 month lagged, 12 month SMAs. We lagged time-updated cumulative bacterial pneumonia episodes by 12 months.

We then fit separate multivariable Cox proportional hazards regression models for each of these primary time-updated exposure variables, parameterised as categorical variables and adjusted for demographics, smoking status, alcohol and drug use disorders, COPD, occupational lung disease, and hepatitis C virus status. We examined the Akaike information criteria (AIC) value for each model to select the time-updated laboratory variables according to lagged versus cumulative, lag (12, 24, or 36 months), and duration of SMAs (12 or 24 months) associated with the best model fit (lowest AIC).¹⁸ We calculated 95% CIs for hazard ratios (HRs) and two-sided p values for trend for CD4 cell count, CD8 cell count, CD4/CD8 ratio, and cumulative bacterial pneumonia episodes by including categorical variables in models as single-term ordinal variables. We then included the primary exposure variables that were significant in separate, best-fitting models in a single, mutually adjusted model to assess the independent associations of these exposures with risk of lung cancer. We confirmed Cox model assumptions by examining plots of Martingale and Schoenfeld residuals and assessing follow-up time interactions.

We did a post-hoc exploratory analysis to assess the relation between the most robust predictors and risk of lung cancer as a function of lag time, restricting the analytic cohort to patients for whom at least 5 years of follow-up data were available. We fit separate multivariable Cox models lagged by 24 months, 36 months, and 48 months. Finally, we did a sensitivity analysis in which we assessed our mutually adjusted model in people whose entry date was after Dec 31, 2001, to assess our findings later in the ART era.

Smoking status was missing for 1108 patients. We fit all models with both the complete case method and multiple imputation to estimate missing values. Results did not meaningfully differ; we report the results of our multiple-imputation models. All analyses were done with SAS (v 9.4).

Role of the funding source

The sponsor had no role in study design; data collection, analysis, or interpretation; or writing of the Article. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Our analytic cohort included 21 666 patients with HIV with a median number of 3·0 (IQR 2·1–3·7) measurements of CD4 cell counts per year (9442 patients were excluded because they had a prevalent lung cancer diagnosis or less than 3 years' follow-up was available, and a further 9865 were excluded because laboratory data were incomplete during the study period). We noted 277 (1·3%) incident cases of lung cancer during the follow-up period (median 7·4 years [IQR 4·6–11·3]). Patients who developed lung cancer were significantly more likely to be older, non-Hispanic white, and current smokers, less likely to have never smoked, and more likely to have been diagnosed with COPD or occupational lung disease than were those who did not develop lung cancer (table 1). Baseline CD4/CD8 ratio was lower in patients who eventually developed lung cancer than in those who did not ($p=0·01$; table 1).

For laboratory markers (CD4 cell count, CD8 cell count, CD4/CD8 ratio, HIV RNA), time-updated longitudinal exposures represented by 12 month lagged values or 12 month lagged, 24 month SMAs were associated with the best model fits according to the AIC (data not shown), so we focused further assessments on these exposure representations. Furthermore, in models including both lagged and cumulative exposures, lagged exposures did not retain significance (data not shown).

Among immune markers, time-updated CD4 cell count and CD4/CD8 ratio, either lagged or SMA, were significantly associated with risk of incident lung cancer in separate models, after adjustment for potential confounding factors (table 2). Specifically, for cumulative exposures, time-updated 12 month lagged, 24 month SMAs of CD4 counts of 100–199 cells per μ L and 200–500 cells per μ L were associated with increased risk of lung cancer compared with counts of greater than 500 cells per μ L (p trend=0·001; table 2), and time-updated 12 month lagged, 24 month SMAs of CD4/CD8 ratios less than 0·4 and ratios of 0·4–1·0 were associated with increased lung-cancer risk compared with ratios greater than 1·0 (p trend=0·0001; table 2).

In separate models after adjustment for potential confounders, we observed significant associations between risk of lung cancer and time-updated HIV RNA lagged by 12 months ($p=0·02$), time-updated 12 month lagged, 24 month SMAs of HIV RNA ($p=0·004$), and 12 month lagged cumulative bacterial pneumonia episodes (p trend=0·0004; table 2).

Significant adjustment covariates in this model were age, current smoking, former smoking, and COPD. When we included the significant time-updated cumulative exposure variables from the separate models (ie, CD4 cell count, CD4/CD8 ratio, HIV RNA, and bacterial pneumonia) in a single, mutually adjusted model also adjusted for potential confounders, the 12 month lagged, 24 month SMAs of CD4/CD8 ratio retained significance (p -trend=0·003), as did cumulative bacterial pneumonia episodes (p trend=0·004).

In our post-hoc exploratory analysis, which included 12 803 patients with HIV (with 170 incident lung cancers), 24 month SMAs of CD4/CD8 ratios were a robust predictor of lung-cancer risk, with ratios less than 0·4 associated with increased risk compared with ratios greater than 1·0, irrespective of the lag (table 3). Cumulative episodes of bacterial

pneumonia were also predictive of lung-cancer risk at all time lags (table 3). In our sensitivity analysis of people with entry dates after 2001, the 12 month lagged, 24 month SMAs of the CD4/CD8 ratio remained significant ($p=0.02$), and cumulative bacterial pneumonia was borderline significant ($p=0.05$).

Discussion

In our large HIV cohort from the ART era, we found that cumulative exposure to low CD4/CD8 ratio was the strongest and most robust independent immunological predictor of increased risk of lung cancer. Our findings suggest that HIV-related immune dysfunction, as measured by CD4/CD8 ratio in particular, and bacterial pneumonia could have a role in the development of lung cancer in people with HIV and could explain some of the increased risk of lung cancer in this population.

Cell-mediated immunity seems to play a part in both lung-cancer surveillance and progression.^{19,20} Therefore, the relation between HIV-related immunosuppression (as measured by CD4 cell count) and risk of lung cancer has been a subject of investigation. Early studies of static, baseline CD4 cell count exposure⁸ and more recent studies including longitudinal CD4 cell count exposure showed no association with lung-cancer risk,^{9,21} perhaps because sample sizes were small (<70 cases of lung cancer in each study). By contrast, a larger study of time-updated longitudinal CD4 cell count in relation to lung-cancer risk showed that the most recently measured count was the strongest predictor of risk.⁷ In a subsequent analysis,²² the investigators showed that participants whose CD4 cell counts did not recover to more than 500 cells per μ L were more likely to develop lung cancer than those whose cell counts recovered. However, lagged measures were not used in either analysis to capture exposures that occurred during the period of carcinogenesis or to account for the possibility that falling CD4 cell counts could be related to undiagnosed lung cancer.

We found that a low cumulative CD4/CD8 ratio was a robust predictor of lung-cancer risk, even after adjustment for known lung-cancer risk factors and cumulative CD4 cell count exposure. Low CD4/CD8 ratio is often present in untreated patients with HIV¹⁴ as a result of declining CD4 cell counts in conjunction with increases in CD8 cells.¹³ In some patients, ART leads to an increase in CD4 cell count without a concomitant fall in CD8 cell count.¹³ Several studies have linked persistently low CD4/CD8 ratio to increased non-AIDS morbidity and mortality, including cancer,^{13,14} and in one study²³ in which CD4/CD8 ratio was not recorded, an association between high CD8 cell count and non-AIDS mortality was noted. Furthermore, CD4/CD8 ratio was the strongest correlate of overall T-cell pathogenesis,²⁴ and a low CD4/CD8 ratio is thought to represent dysfunctional immune activation associated with chronic inflammation.¹³ In our cohort, which includes a high proportion of patients taking ART, the persistently low CD4/CD8 ratio could reflect this inflammatory syndrome.

The second robust predictor of risk of lung cancer was cumulative bacterial pneumonia episodes. Bacterial pneumonia has been linked to lung cancer in the setting of HIV in previous studies.^{4,6} Pneumonia risk is increased in HIV infection¹⁰ (particularly in patients

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

with low CD4 cell counts), and the resultant inflammatory injury could contribute to the causal pathways leading to the excess lung-cancer risk in people with HIV.⁶ Furthermore, dysfunctional immune activation could lead to more deleterious inflammatory responses to bacterial pneumonia in patients with HIV than in those without HIV.²⁵ Previous studies had limited power or data to disentangle the effects of pneumonia and CD4 cell count on subsequent risk of lung cancer. In our mutually adjusted model, bacterial pneumonia retained significance, but CD4 cell count did not. Thus, the relation between CD4 cell count and lung-cancer risk might be confounded or mediated by bacterial pneumonia. Our results suggest that prevention of bacterial pneumonia via early initiation of ART or pneumococcal vaccination, which is already recommended for many people with HIV, could contribute to prevention of lung cancer.

The factors that were related to increased incidence of lung cancer (ie, low CD4 cell count, low CD4/CD8 ratio, increased HIV RNA concentrations, and bacterial pneumonia) in our study are all associated with increased risk of mortality, which makes death an important competing risk. Therefore many patients affected by these factors probably could have eventually developed lung cancer if they had lived, suggesting that the effects of these factors might be greater than was recorded in our analysis.

Smoking cessation is a crucial component of primary prevention of lung cancer. Additionally, early detection of lung cancer with low dose CT could be a safe and effective approach to secondary prevention in people with HIV.²⁶ CD4/CD8 ratio and bacterial pneumonia, along with traditional risk factors (eg, smoking, age, COPD), which were more strongly associated with lung-cancer risk than CD4/CD8 ratio and bacterial pneumonia, could potentially be used to risk-stratify patients with HIV for targeted lung-cancer screening.

Our study had a large, national cohort with long-term follow-up and a lot of pathologically confirmed lung cancers. We used lagged measures to attempt to capture exposures that occurred during the period of carcinogenesis and to exclude possible immunological changes (ie, decline in CD4 cell count) caused by the presence of preclinical lung cancer. Data from large lung-cancer screening studies in people without HIV have been used to estimate the so-called preclinical sojourn time for undiagnosed cancers (ie, the amount of time between development of a new cancer and clinical diagnosis) to be 1–3 years.²⁷

Our study had several limitations. First, our cohort was comprised solely of US veterans with HIV and was nearly exclusively male. Therefore our results might not be generalisable to other people with HIV. However, our cohort did include a large proportion of patients from racial and ethnic minorities, who are underrepresented in other large US HIV cohorts. Our ascertainment of cancer diagnoses was limited to Veterans Affairs sources, and therefore cancers diagnosed and treated outside the Veterans Affairs system were not included. However, by restricting our sample to patients with frequent laboratory measurements and therefore a high level of engagement with Veterans Affairs care, we probably minimised this potential bias, although these restrictions might also have limited the generalisability of our results. Thus, excluded patients differed from included patients in most characteristics: they were less healthy and had lower CD4 cell counts, higher HIV RNA concentrations, more

bacterial pneumonias, and were more likely to die during follow-up (appendix p 1). In addition to potentially affecting generalisability, our strict inclusion criteria might have introduced selection bias.

A further limitation was the lack of detailed smoking history (and the absence of data for other smoked or inhaled drugs such as marijuana or cocaine) and time-updated assessment of smoking status. However, previous studies have not shown associations between smoking and declines in CD4 cell count²⁸ or low CD4/CD8 ratio²⁹ in people with HIV, and the results of an investigation in people without HIV suggested that smoking might be associated with increased CD4/CD8 ratios.³⁰ Thus, meaningful residual confounding by smoking might not have occurred in our study.

We used data from a large HIV cohort to show that several measures of cumulative exposure to impaired immune function are associated with increased risk of lung cancer after adjustment for confounders. Cumulative CD4/CD8 ratio and episodes of bacterial pneumonia were the most robust predictors of lung-cancer risk. If our findings are confirmed, CD4/CD8 ratio and history of bacterial pneumonia, along with smoking, age, and COPD, could be used to target high-risk groups with lung-cancer prevention measures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was supported by the National Cancer Institute (K07 CA180782 to KS, R01 CA173754 to JW and KC, and R01 CA165937 to RD) and the National Institute on Alcohol and Alcohol Abuse (U01 AA020794, U01 AA013566, and U01AA020790). We are grateful to the US Veterans Affairs Central Cancer Registry (VACCR) for linking the Veterans Aging Cohort Study Virtual Cohort with the VACCR database and providing us with a dataset containing the linked records. The views expressed in this Article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs.

References

1. Engels EA, Pfeiffer RM, Goedert JJ, et al. Trends in cancer risk among people with AIDS in the United States 1980–2002. *AIDS*. 2006; 20:1645–54. [PubMed: 16868446]
2. Simard EP, Engels EA. Cancer as a cause of death among people with AIDS in the United States. *Clin Infect Dis*. 2010; 51:957–62. [PubMed: 20825305]
3. Shieh MS, Pfeiffer RM, Gail MH, et al. Cancer burden in the HIV-infected population in the United States. *JNCI*. 2011; 103:753–62. [PubMed: 21483021]
4. Sigel K, Wisnivesky J, Gordon K, et al. HIV as an independent risk factor for incident lung cancer. *AIDS*. 2012; 26:1017–25. [PubMed: 22382152]
5. Silverberg MJ, Chao C, Leyden WA, et al. HIV infection, immunodeficiency, viral replication, and the risk of cancer. *Cancer Epidemiol Biomarkers Prev*. 2011; 20:2551–59. [PubMed: 22109347]
6. Shebl FM, Engels EA, Goedert JJ, Chaturvedi AK. Pulmonary infections and risk of lung cancer among persons with AIDS. *J Acquir Immune Defic Syndr*. 2010; 55:375–79. [PubMed: 20736841]
7. Guiquet M, Boué F, Cadranel J, Lang J-M, Rosenthal E, Costagliola D. Effect of immunodeficiency, HIV viral load, and antiretroviral therapy on the risk of individual malignancies (FHDH-ANRS CO4): a prospective cohort study. *Lancet Oncol*. 2009; 10:1152–59. [PubMed: 19818686]
8. Engels EA, Brock MV, Chen J, Hooker CM, Gillison M, Moore RD. Elevated incidence of lung cancer among HIV-infected individuals. *J Clin Oncol*. 2006; 24:1383–88. [PubMed: 16549832]

9. Clifford GM, Lise M, Franceschi S, et al. Lung cancer in the Swiss HIV Cohort Study: role of smoking, immunodeficiency and pulmonary infection. *Br J Cancer*. 2012; 106:447–52. [PubMed: 22240797]
10. Benard A, Mercie P, Alioum A, et al. Bacterial pneumonia among HIV-infected patients: decreased risk after tobacco smoking cessation. *ANRS CO3 Aquitaine Cohort*, 2000–2007. *PloS One*. 2010; 5:e8896. [PubMed: 20126646]
11. Brenner DR, McLaughlin JR, Hung RJ. Previous lung diseases and lung cancer risk: a systematic review and meta-analysis. *PloS One*. 2011; 6:e17479. [PubMed: 21483846]
12. Strindhall J, Skog M, Ernerudh J, et al. The inverted CD4/CD8 ratio and associated parameters in 66-year-old individuals: the Swedish HEXA immune study. *Age*. 2013; 35:985–91. [PubMed: 22415616]
13. Serrano-Villar S, Sainz T, Lee SA, et al. HIV-infected individuals with low CD4/CD8 ratio despite effective antiretroviral therapy exhibit altered T cell subsets, heightened CD8+ T cell activation, and increased risk of non-AIDS morbidity and mortality. *PLoS Pathogens*. 2014; 10:e1004078. [PubMed: 24831517]
14. Serrano-Villar S, Perez-Elias MJ, Dronda F, et al. Increased risk of serious non-AIDS-related events in HIV-infected subjects on antiretroviral therapy associated with a low CD4/CD8 ratio. *PloS One*. 2014; 9:e85798. [PubMed: 24497929]
15. Park LS, Tate JP, Rodriguez-Barradas MC, et al. Cancer incidence in HIV-infected versus uninfected veterans: comparison of cancer registry and ICD-9 code diagnoses. *J AIDS Clin Res*. 2014; 5:1000318. [PubMed: 25580366]
16. Losina E, Yazdanpanah Y, Deuffic-Burban S, et al. The independent effect of highly active antiretroviral therapy on severe opportunistic disease incidence and mortality in HIV-infected adults in Cote d'Ivoire. *Antivir Ther*. 2007; 12:543–51. [PubMed: 17668563]
17. Helleberg M, Kronborg G, Larsen CS, et al. CD4 decline is associated with increased risk of cardiovascular disease, cancer, and death in virally suppressed patients with HIV. *Clin Infect Dis*. 2013; 57:314–21. [PubMed: 23575194]
18. Bradburn MJ, Clark TG, Love SB, Altman DG. Survival analysis Part III: multivariate data analysis—choosing a model and assessing its adequacy and fit. *Br J Cancer*. 2003; 89:605–11. [PubMed: 12915864]
19. Remark R, Becker C, Gomez JE, et al. The non-small cell lung cancer immune contexture. A major determinant of tumor characteristics and patient outcome. *Am J Respir Crit Care Med*. 2015; 191:377–90. [PubMed: 25369536]
20. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med*. 2015; 373:1627–39. [PubMed: 26412456]
21. Kesselring A, Gras L, Smit C, et al. Immunodeficiency as a risk factor for non-AIDS-defining malignancies in HIV-1-infected patients receiving combination antiretroviral therapy. *Clin Infect Dis*. 2011; 52:1458–65. [PubMed: 21628488]
22. Hleyhel M. Cancer Risk Group of the French Hospital Database on HIV. Risk of non-AIDS-defining cancers among HIV-1-infected individuals in France between 1997 and 2009: results from a French cohort. *AIDS*. 2014; 28:2109–18. [PubMed: 25265077]
23. Helleberg M, Kronborg G, Ullum H, Ryder LP, Obel N, Gerstoft J. Course and clinical significance of CD8+ T-cell counts in a large cohort of HIV-infected individuals. *J Infect Dis*. 2015; 211:1726–34. [PubMed: 25489001]
24. Buggert M, Frederiksen J, Noyan K, et al. Multiparametric bioinformatics distinguish the CD4/CD8 ratio as a suitable laboratory predictor of combined T cell pathogenesis in HIV infection. *J Immunol*. 2014; 192:2099–108. [PubMed: 24493822]
25. Rubbo PA, Tuaillet E, Bollore K, et al. The potential impact of CD4+ T cell activation and enhanced Th1/Th2 cytokine ratio on HIV-1 secretion in the lungs of individuals with advanced AIDS and active pulmonary infection. *Clin Immunol*. 2011; 139:142–54. [PubMed: 21345739]
26. Makinson A, Le Moing V, Reynes J, et al. Lung cancer screening with chest computed tomography in people living with HIV. A review by the multidisciplinary CANCERVIH Working Group. *J Thorac Oncol*. 2016; 11:1644–52. [PubMed: 27449803]

27. Wu D, Erwin D, Rosner GL. Sojourn time and lead time projection in lung cancer screening. *Lung Cancer*. 2011; 72:322–26. [PubMed: 21075475]
28. Kabali C, Cheng DM, Brooks DR, Bridden C, Horsburgh CR Jr, Samet JH. Recent cigarette smoking and HIV disease progression: no evidence of an association. *AIDS Care*. 2011; 23:947–56. [PubMed: 21400309]
29. Craib KJ, Schechter MT, Montaner JS, et al. The effect of cigarette smoking on lymphocyte subsets and progression to AIDS in a cohort of homosexual men. *Clin Invest Med*. 1992; 15:301–08. [PubMed: 1516287]
30. Tollerud DJ, Clark JW, Brown LM, et al. The effects of cigarette smoking on T cell subsets. A population-based survey of healthy caucasians. *Am Rev Respir Dis*. 1989; 139:1446–51. [PubMed: 2786361]

Table 1

Baseline characteristics of patients with HIV, by lung cancer diagnosis

	Lung cancer diagnosed (n=277)	No lung cancer (n=21 389)	p value
Median age, years (IQR)	50 (46–57)	45 (39–52)	<0.0001
Male sex	273 (99%)	20 867 (98%)	0.3
Race			0.02
Non-Hispanic white	128 (46%)	8731 (41%)	
Non-Hispanic black	132 (48%)	10 176 (48%)	
Hispanic	12 (4%)	1657 (8%)	
Other	5 (2%)	825 (4%)	
Smoking status			<0.0001
Current smoker	201 (73%)	11 527 (54%)	
Former smoker	41 (15%)	3102 (15%)	
Never smoked	14 (5%)	5673 (27%)	
Unknown	21 (8%)	1087 (5%)	
Drug use disorders	38 (14%)	3527 (16%)	0.2
Alcohol use disorders	47 (17%)	2991 (14%)	0.2
CD4 cell count (per µL)			0.2
<100	40 (14%)	3031 (14%)	
100–199	47 (14%)	2882 (13%)	
200–500	115 (42%)	9029 (42%)	
>500	75 (30%)	6447 (30%)	
CD8 cell count (per µL)			0.07
<600	75 (27%)	6294 (29%)	
600–1000	83 (30%)	7323 (34%)	
>1000	119 (43%)	7772 (36%)	
CD4/CD8 ratio			0.01
<0.4	143 (52%)	9763 (46%)	
0.4–1.0	116 (42%)	9177 (43%)	
>1.0	18 (6%)	2449 (11%)	
HIV RNA (copies per mL)			0.6
<500	111 (40%)	8874 (41%)	
500	166 (60%)	12 515 (59%)	
Antiretroviral therapy	225 (81%)	16 577 (78%)	0.1
Protease inhibitor	124 (45%)	8679 (41%)	0.3
Non-nucleoside reverse transcriptase inhibitor	85 (31%)	5627 (26%)	0.2
Integrase inhibitor	1 (<1%)	100 (<1%)	0.5

	Lung cancer diagnosed (n=277)	No lung cancer (n=21 389)	p value
Nucleoside reverse transcriptase inhibitor	221 (80%)	15 080 (71%)	0.001
Unknown	16 (6%)	3015 (14%)	<0.0001
Hepatitis C virus infection	83 (30%)	5974 (28%)	0.5
Chronic obstructive pulmonary disease	35 (13%)	792 (4%)	<0.0001
Occupational lung disease	3 (1%)	54 (<1%)	0.01
Pulmonary infections			
<i>Pneumocystis jirovecii</i> pneumonia	9 (3%)	727 (3%)	0.9
Tuberculosis	6 (2%)	242 (1%)	0.1
Bacterial pneumonia	17 (6%)	1034 (5%)	0.3
Died during follow-up	218 (79%)	5284 (25%)	<0.0001

Data are n (%), unless otherwise specified.

Sigel et al. HRs for incidence of lung cancer for time-updated longitudinal exposure variables in separate and mutually adjusted Cox proportional hazards regression models

Table 2

	Cases of lung cancer with exposure (n=277)	Separate models*		Mutually adjusted model†	
		HR (95% CI)	p trend	HR (95% CI)	p trend
CD4 cell count (per μL)					
12 month lagged			0.001		
<100	12	1.1 (0.6-2.3)			
100-199	31	2.3 (1.6-3.4)			
200-500	147	1.2 (1.2-2.1)			
>500‡	87	1			
12 month lagged (24 month SMA)			0.9		
<100	8	1.0 (0.5-2.1)		0.7 (0.3-1.5)	
100-199	40	2.1 (1.4-3.1)		1.5 (0.9-2.3)	
200-500	146	1.6 (1.2-2.1)		1.3 (0.9-1.7)	
>500‡	83	1		1	
CD8 cell count (per μL)					
12 month lagged			0.05		
>1000	121	1.5 (0.9-2.1)			
600-1000	93	1.4 (1.0-2.3)			
<600‡	63	1			
12 month lagged (24 month SMA)			0.05		
>1000	125	1.6 (1.0-2.4)			
600-1000	102	1.6 (0.9-2.3)			
<600‡	50	1			
CD4/CD8 ratio					
12 month lagged			0.001		
<0.4	133	2.6 (1.6-4.1)			

		Cases of lung cancer with exposure (n=277)	Separate models*			Mutually adjusted model†		
			HR (95% CI)	p trend	HR (95% CI)	p trend	HR (95% CI)	p trend
0.4-1.0	125	1.9 (1.2-3.0)						
>1.0‡	19	1						
12 month lagged (24 month SMA)								
<0.4	134	3.5 (2.0-6.1)					2.6 (1.4-4.9)	
0.4-1.0	129	2.8 (1.6-4.9)					2.4 (1.4-4.3)	
>1.0‡	14	1					1	
HIV RNA (copies per mL)								
12 month lagged								
500	96	1.4 (1.1-1.9)					0.02§	
<500‡	181	1						
12 month lagged (24 month SMA)								
500	144	1.5 (1.1-1.9)					0.004§	
<500‡	133	1					1	
Bacterial pneumonia								
12 month lagged (cumulative episodes)								
2 episodes	14	1.8 (1.0-2.5)					1.6 (0.9-2.9)	
1 episode	46	1.7 (1.2-2.4)					1.3 (1.1-2.3)	
0 episodes‡	217	1					1	

All models were adjusted for age, race or ethnicity, smoking status, alcohol use disorders, drug use disorders, chronic obstructive pulmonary disease, occupational lung disease, and hepatitis C virus infection. HR=hazard ratio. SMA=simple moving average.

* Each separate model includes one time-updated exposure variable (eg, 12 month lagged CD4 cell count).

† Includes time-updated cumulative exposure variables significant in the separate models (ie, 12 month lagged and 24 month moving average CD4 cell count, CD4/CD8 ratio, and HIV RNA, and 12 month lagged cumulative episodes of bacterial pneumonia). Significant adjustment covariates in this model were age (HR 1.08 per 1-year increase, 95% CI 1.06-1.09), Hispanic ethnicity (HR compared with white race 0.4, 95% CI 0.2-0.9), current smoking (HR compared with never smoking 8.5, 95% CI 4.9-14.8), former smoking (HR compared with never smoking 4.0, 95% CI 2.1-7.3), and chronic obstructive pulmonary disease (HR 4.4, 95% CI 1.1-18.3).

‡ Reference category from which HRs are calculated.

§ p value and not p trend, is reported for HIV RNA.

Table 3

HRs for incidence of lung cancer associated with time-updated 24 month SMA of the CD4/CD8 ratio and cumulative bacterial pneumonia episodes with different lags in separate Cox proportional hazards regression models

CD4/CD8 ratio (24 month SMA)		
	HR (95% CI)	p trend
24 month lag		<0.0001
<0.4	5.0 (2.3–10.7)	
0.4–1.0	3.1 (1.4–6.7)	
>1.0 *	1	
36 month lag		<0.0001
<0.4	3.9 (1.9–8.1)	
0.4–1.0	2.4 (1.2–5.1)	
>1.0 *	1	
48 month lag		0.001
<0.4	3.5 (1.7–7.1)	
0.4–1.0	2.3 (1.1–4.7)	
>1.0 *	1	
Bacterial pneumonia		
24 month lag		0.0002
2 episodes	2.3 (1.2–4.3)	
1 episode	1.9 (1.3–2.9)	
0 episodes *	1	
36 month lag		0.005
2 episodes	2.7 (1.4–5.5)	
1 episode	1.8 (1.2–2.9)	
0 episodes *	1	
48 month lag		0.01
2 episodes	2.1 (0.9–5.2)	
1 episode	1.7 (1.1–2.8)	

	HR (95% CI)	p trend
0 episodes *	1	

Subcohorts with at least 5 years' follow-up were used for these analyses. Each model was adjusted for age, race or ethnicity, smoking status, alcohol use disorders, drug use disorders, chronic obstructive pulmonary disease, occupational lung disease, and hepatitis C virus infection. HR=hazard ratio. SMA=simple moving average.

* Reference category from which HRs are calculated.